patient compliance. Women who abandoned the use of these oral contraceptives in clinical trials primarily cited weight gain or headaches as an undesired effect. As with other available birth control pills, nausea and mood changes were also cited. A risk of breast cancer in oral contraceptive users remains inconclusive and a source of patients' concern. There is some tentative evidence that gestodene mimics the effects of tamoxifen and therefore may actually reduce the risks of both breast cancer and benign breast disease.

With efficacy matching other available products, the new oral contraceptives offer enhanced patient compliance through the reduction of undesired breakthrough bleeding and amenorrhea. Their metabolic neutrality offers safety that equals or possibly surpasses that of other available contraceptives. Thus, they provide a good first choice for patients and an alternative for women experiencing problems with currently available oral contraceptives. Patients doing well on current formulations should not switch without indication.

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Premenstrual Syndrome

PREMENSTRUAL PHYSICAL and emotional changes occur in as many as 80% of women of reproductive age. The most common symptoms include fatigue, depression, irritability, breast tenderness, swelling, and food cravings. Estimates regarding the prevalence of the premenstrual syndrome (PMS) generally agree that 20% to 40% of these women experience some difficulty as a result of these changes during the premenstrual time interval, and 2.5% to 5% report a notable effect on work or life-style.

The diagnosis of PMS depends on the exclusion of other coexisting medical disorders. Although its incidence in the general population is high, most women do not have this condition as a chief complaint. Of those who do present with PMS, coexisting medical and psychiatric disorders are observed with startling frequency. The most important aid to clinicians in the diagnosis of PMS is the use of a monthly symptom rating inventory. Such inventories should reveal a relatively symptom-free interval from cycle day 4 through cycle day 12 and at least a 30% higher symptoms score in the late luteal phase (last seven days of the cycle) as compared with the midfollicular phase (cycle days 3 through 9). At least 25% of women having PMS-like symptoms will have no such symptom-free interval, suggesting the need for further medical and psychiatric evaluation, particularly for affective disorder, panic disorder, and personality disorder. An ultrasensitive thyrotropin level should also be obtained to screen for thyroid disorder. The incidence of perimenopausal symptoms is also high in this population, and a serum follicle-stimulating hormone level may be helpful in establishing the latter diagnosis. A substantial number of women have PMS symptoms while taking oral contraceptives. In these women, the oral contraceptive drug should be discontinued and symptoms prospectively evaluated while they use barrier contraception.

In a substantial number of women, symptoms are not adequately controlled by exercise, the elimination of caffeine and chocolate, and diuretic therapy. Recent evidence provides strong support for the hypothesis that progesterone modulates central neurotransmitter activity within the opioidergic, serotonergic, and γ-aminobutyric acid (GABA)-ergic systems. The currently accepted hypothesis of PMS is that progesterone acting through these central neurotransmitter alterations causes the behavioral symptoms of PMS. At present, although there is no safe way to intervene directly into the opioidergic system, double-blind placebo-controlled studies have shown a pronounced reduction of PMS symptoms using the serotonin uptake inhibitor, fluoxetine hydrochloride, at a dose of 20 mg daily throughout the menstrual cycle. Similarly, several double-blind studies have shown marked benefit using alprazolam, a benzodiazepine that acts on the GABA-receptor complex, in doses of 0.25 mg four times a day during the last week of the menstrual cycle. The addiction potential of alprazolam mandates that it be reserved for reliable patients and restricted to the latter part of the menstrual cycle. Nonetheless, these therapies provide the first conclusively proven beneficial therapy for PMS.

At least three studies have shown the efficacy of long-acting gonadotropin-releasing hormone agonists in premenstrual syndrome. Until the problems of resultant osteoporosis are overcome, however, this agent must be limited to short-term use.

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Therapeutic Options for Ectopic Pregnancy

THE ABILITY to detect ectopic pregnancies early with the aid of sensitive β-human chorionic gonadotropin (β-HCG) assays and intravaginal sonography has increased the options for treatment. Whereas exploratory laparotomy was once the standard, laparoscopic management and medical therapy are now used more frequently.

The goals of both laparoscopic and medical therapy are to treat before substantial tubal destruction has occurred and to eliminate the increased risk, discomfort, and longer hospital stays associated with laparotomy. With the use of intravaginal sonography, an intrauterine pregnancy should be detectable in a patient with a β-HCG value of 1,000 to 2,000 IU per liter (International Reference Preparation standard) or greater. The exact value for this "discriminatory zone" will be a function of the reference standard being used, the resolution of the ultrasound equipment, and the skill of the ultrasonographer. Serial values of β-HCG may be followed both to look for an appropriate rise of greater than 66% every 48 hours, suggesting a viable intrauterine pregnancy, and to reach the "discriminatory zone."

When an intrauterine pregnancy is excluded, laparoscopy can then be done to both diagnose and treat the ectopic pregnancy. A linear salpingostomy, segmental resection, or salpingectomy can be done safely through a laparoscope de-

pending on the size of the pregnancy, the patient's desire for future fertility, and the ability to control hemostasis. Laparoscopic therapy will generally require a primary infraumbilical incision for the laparoscope and two or more smaller incisions in the suprapubic region for ancillary trocars. The outcome of subsequent pregnancies for women treated laparoscopically for the ectopic pregnancies is similar to that achieved by traditional exploratory laparotomy. There is a persistence rate of about 5% with laparoscopic salpingostomy, so these patients must be observed postoperatively with serial β-HCG measurements.

Medical therapy with methotrexate may be used first or to treat patients with persistently elevated β-HCG values after laparoscopic salpingostomy. One regimen is to give methotrexate, 1.0 mg per kg, and leucovorin calcium (citrovorum factor), 0.1 mg per kg, on alternating days until the β-HCG values decrease by 15% on two consecutive days. A maximum of four doses can be used consecutively. Criteria for medical therapy include hemodynamic stability, the absence of hepatic or renal disease, certain diagnosis (when a nonviable intrauterine pregnancy has been ruled out), and an adnexal mass measuring less than 3.5 cm sonographically in its greatest dimension. These patients should be counseled and observed closely with β-HCG values and liver function tests because about 4% will have tubal rupture and require surgical management. Results as measured by the patency of fallopian tubes by hysterosalpingogram and by subsequent pregnancy seem to compare favorably with surgical management.

Laparoscopic therapy and medical therapy for ectopic pregnancy are important advances because of their favorable patient acceptance and the potential effect on the economics of health care.

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Genetic Predisposition to Ovarian Cancer

OVARIAN CANCER remains the most common cause of death from gynecologic malignancy in developed countries. It was estimated that in 1991 20,700 new cases and about 13,000 deaths would occur in the United States alone. The "lifetime risk" of ovarian cancer developing in a woman in the United States is about 1.4%, with the vast majority of tumors (85% to 90%) being epithelial in origin.

Although the cause of ovarian carcinoma remains unclear, genetic susceptibility is an important risk factor. Pedigree analysis has revealed three distinct patterns of familial transmission involving epithelial ovarian cancer. The most common syndrome is site-specific, and the heritable risk is limited to cancer of the ovary. The second is often referred to as the breast-ovarian carcinoma syndrome, and women in these families are at increased risk for one or both cancers developing. The cancer family syndrome also involves ovarian cancer in association with endometrial, breast, and colon carcinomas.

The pattern of transmission for each is autosomal dominant with variable penetrance. Women with two or more first-degree relatives with ovarian carcinoma have as much as a 50% risk of becoming affected. An important factor is that in the first two syndromes, men may be carriers of the gene and can transmit it to half of their offspring. In the cancer family syndrome (Lynch syndrome II), men are also at risk for adenocarcinomas, especially colorectal, and transmit the deleterious gene to half of their daughters and sons. It is currently impossible to quantitate the risk in a woman with one first-degree relative or second-degree relatives who have ovarian cancer, although it is safe to say that it is greater than that in the population as a whole. Careful surveillance should begin in women in their early 20s.

The genetics of ovarian carcinoma have not been well described. A loss of alleles on chromosomes 1, 3, 6, 11, and 17 has been detected, which may represent the deletion of tumor-suppressor genes. The amplification of several protooncogenes has also been described.

Many physicians advise prophylactic oophorectomy for women at risk for familial ovarian cancer. The age of onset is significantly lower in patients with hereditary ovarian carcinoma, and, this being the case, oophorectomy is often done as soon as childbearing is completed. It has been recommended that routine pelvic examinations be expanded to include annual pelvic ultrasonography and the assessment of serum CA 125 levels starting at age 25 for women in this high-risk group. Unfortunately, oophorectomy does not offer complete protection. Adenocarcinoma of the mesothelium, which is histologically indistinguishable from ovarian cancer, has occurred in several patients.

Genetic risk factors account for only a small proportion of all patients with cancer of the ovaries, with estimates as high as 10% but more likely 3% to 5%. Still, this group represents a population that is important in terms of surveillance, prevention, and as an opportunity to further our understanding of this disease.

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Ovarian Cancer Screening

SCREENING FOR ovarian cancer has begun to receive a great deal of publicity both within the areas of clinical research and in the news media. This is undoubtedly due in part to the tragic and well-publicized deaths of young women with advanced disease; it is also likely caused by the frustration of dealing with a cancer that will strike more than 20,000 women annually, leaving about 13,000 dead. Because these cancers are detected in later stages, those afflicted have only a 13% to 20% chance of surviving five years. The early detection of other cancers has increased survival. Recommendations for ovarian cancer screening are aimed at detecting ovarian cancer at earlier stages in hopes of prolonging survival.

Tools now widely available for screening include the biochemical marker, CA 125, and ultrasonography. CA 125 represents an antigen to the coelomic epithelial derivatives and is measured in the serum using a monoclonal antibody. Its greatest use thus far is in the management of ovarian cancer patients with respect to regression or progression of